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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/609,019	06/26/2003	Richard K. Cooper	51687-0101 (287015)	8431

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EXAMINER

PARAS JR, PETER

ART UNIT

PAPER NUMBER

1632

DATE MAILED: 12/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/609,019

Applicant(s)

COOPER ET AL.

Examiner

Peter Paras, Jr.

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 January 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-51 is/are pending in the application.
- 4a) Of the above claim(s) 22-51 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-21 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 26 June 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
- 4) ☐ Interview Summary (PTO-413)
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____
- Paper No(s)/Mail Date 11/26/2003, 3/24/04, 5/13/04, 5/27/04, 12/16/04, 11/3/05

DETAILED ACTION

Claims 1-51 are pending.

Applicant is reminded of the duty to disclose information, which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, 1.56(a), including related patent applications.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 1-21, drawn to a vector, classified in class 435, subclass 320.1.
- II. Claims 22-51, drawn to a method for producing a transgenic animal and a method of producing a desired protein comprising creating a transgenic animal and isolating said protein from the animal, classified in classes 800 and 800, subclasses 4 and 25.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP 821.04. Process claims that depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR I .104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See Guidance on Treatment of Product and Process Claims in light of *In re Ochiai*, *In re Brouwer* and 35 U.S.C. 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. Failure to do so may result in a loss of the right to rejoinder. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP 804.01.

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the product as claimed can

be used in a materially different process. For example, the vector of Group I can be used to transform somatic cells *in vitro*. Also, transgenic non-human animals can be created with other vectors. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, separate classification and separate search, restriction for examination purposes as indicated is proper.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. However, the claim is not in the first line of the specification. A proper claim for priority should be in the first line of the specification immediately following the Title. Correction is required.

Specification

The disclosure is objected to because of the following informalities: The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification. Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a vector comprising a transposase gene operably linked to a first promoter, one or more genes of interest operably-linked to one or more additional promoters, wherein the genes of interest are flanked by transposase insertion sequences, and wherein the first promoter comprises a modified Kozak sequence comprising ACCATG.

The specification has taught that the claimed invention features a promoter comprising a Kozak sequence that comprises ACCATG. The specification has exemplified the creation of the vector set forth in SEQ ID NO: 1. However, the specification has not provided guidance correlating to insertion of the Kozak sequence ACCATG in a promoter, such that the Kozak sequence functions to initiate translation. Although the specification asserts that the Kozak sequence in SEQ ID NO: 1 is in the promoter region. See page 58 of the specification in lines 7-9, which clearly state bases

ACC were inserted upstream of bases ATG to modify the CMV promoter. It is also stated that the CMV promoter consisted of bases 133-1777, which means that the ACCATG should be located within bases 133-1777. However, when the sequence of SEQ ID NO: 1 was examined the Kozak sequence, ACCATG, actually began at base 1780, which is part of the transposase gene coding sequence. Therefore, it would appear in the absence of evidence to the contrary that the instant specification has not taught a promoter comprising a Kozak sequence.

In any event, it is known in the art that Kozak sequences promote initiation of translation. It is also known in the art the optimal Kozak sequence is ACCATG and that it is located at the translation initiation site of a coding sequence and not in a promoter as the transcription initiation site, where a conventional promoter sequence ends is upstream of the translation initiation site. See Kozak M. (Gene, 1999, 234: 187-208) at page 192, in section 3.3. Therefore, for ACCATG to function as a Kozak sequence it must be at the translation initiation site. However, the specification has not provided guidance for inserting a Kozak sequence in a promoter such that it is functional at the translation initiation site. The specification has merely stated, "a modified Kozak sequence ACCATG was added to the promoter". See the specification at page 55, in lines 16-17. Further, the specification asserted that ACCATG contains the Kozak sequence and the start codon for the transposase. This suggests that ATG is part of the transposase coding sequence and not the promoter. Also, as discussed above the ACCATG according to the sequence listing for SEQ ID NO: 1 is actually located in the transposase gene region. However, the claims require for ACCATG to be in the

promoter, any part of the promoter. The specification has failed to provide guidance or working examples correlating to insertion of ACCATG as a functional Kozak sequence in a promoter. Finally, it would be unpredictable if ACCATG could function as a Kozak sequence when inserted anywhere in a promoter as required by the claims.

Given the lack of guidance provided by the specification it would have required undue experimentation to make and use a promoter comprising a functional Kozak sequence for one of skill in the art without a reasonable expectation of success.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 embraces a promoter comprising a modified Kozak sequence comprising ACCATG. First, the claim is indefinite because it is not clear if the modified sequence is ACCATG or a sequence comprising ACCATG. Moreover, the art has set forth that in vertebrate mRNAs initiation sites usually conform to all or part of the sequence GCCRCCAUG. In particular, the art has set forth that Kozak sequence ACCAUG is optimal for initiation of translation. Finally, since Kozak sequences (all combinations, including ACCAUG) are naturally occurring and found in mRNAs, it is unclear how a Kozak sequence can be modified. In particular, is it not understood from the

specification what the modification embraces or what exactly is a modified Kozak sequence or what it is modified from. See Kozak M. (Gene, 1999, 234: 187-208) at page 192, in section 3.3. Claims 2-21 depend from claim 1.

Claim 1 is directed to a promoter comprising a modified Kozak sequence. The claim as written is unclear. First, it is well known in the art that a Kozak sequence is a sequence found in mRNAs and is associated with initiation of translation and includes the AUG start codon. The claim however requires that the Kozak sequence is only located somewhere in a promoter. For a Kozak sequence to be functional, it needs to be operably linked a coding sequence. If a Kozak sequence is located elsewhere, for example in a non-transcribed promoter region, it will not function as a Kozak sequence and promote initiation of translation. It is not clear from the claim or the specification if the Kozak sequence is upstream or downstream of the start site of transcription. Moreover, the metes and bounds of promoter are not readily apparent, as a promoter comprising a Kozak sequence would include part of the transposase coding sequence. Given the claim language "a transposase gene operably linked to a first promoter" it would appear that the transposase gene and promoter are separate entities. The specification is silent to that end. Therefore, inclusion of a Kozak sequence in a promoter is unclear and renders the claim indefinite. Claims 2-21 depend from claim 1.

Claim 2 embraces modifying one to twenty codons at a beginning of the transposase gene. The claim reads on a transposase gene having more than one beginning. The claim is indefinite, as it is not understood how a gene can have more than one beginning. Moreover, it is not apparent from the specification what region of

the transposase gene "a beginning" encompasses. It is not understood where the beginning of the transposase gene starts and ends. Claim 3 depends from claim 2.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-6, 8-10, 12, and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cooper R. (US 5,719,055) taken with Meiss et al (Biotechniques, 2000, 29(3): 476, 478, and 480).

The claims are directed to a vector comprising a transposase gene operably linked to a first promoter, one or more genes of interest operably-linked to one or more additional promoters, wherein the genes of interest are flanked by transposase insertion sequences, and wherein the first promoter comprises a modified Kozak sequence comprising ACCATG.

Cooper taught a vector comprising a gene encoding a transposase operably linked to a promoter; two transposon insertion sequences recognized by the transposase; and an exogenous gene located between the transposon insertion sequences. The promoter directing expression of the transposase gene may be inducible. See the claims. In column 8, at lines 58-67 Cooper listed transposases, including Tn10 and Tn5, which may be used in combination with the same vector. The

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claims require a modified transposase gene, wherein one to twenty codons, preferably the first ten, at a beginning of the gene are modified by changing a nucleotide at a third base position of the codon to an adenine or thymine without changing the amino acid encoded by the codon. Such claim limitations embrace not only mutated but also wild-type transposase genes. There is no sequence of a starting transposase gene and a resulting modified transposase gene sequence. Therefore, the claim limitations are met by any transposase gene having an A or T in the third position of codons one to twenty at a beginning, preferably the in the first ten codons, of the transposase gene. It would appear inherent that any transposase gene would comprise a codon having an A or T in the third position of codons one to twenty at a beginning, preferably the in the first ten codons. Cooper exemplified use of the Tn10 gene but did not provide its sequence. The Examiner however has provided a partial sequence of a beginning of a Tn5 transposase gene that comprises codons having an A or T in the third position in support of the inherency assertions. See for example, Schulz et al (J. Mol. Biol., 1991, 221: 65-80), which taught a Tn5 gene sequence having codons with an A or T in the third position. See figure 2 on page 69 in particular see the codons immediately upstream or downstream of the AUG codon. Cooper et al discussed use of both constitutive and inducible promoters for directing expression of both the transposase gene and the gene of interest. See for example, columns 15-18. Cooper sought to express transgenes in various vertebrates as evidenced by the teachings in column 9, in lines 40-50. Cooper differed from the claimed invention by not teaching a promoter comprising a modified Kozak sequence that comprises ACCATG or a vector comprising

more than one gene of interest operably linked to more than one promoter between the transposase insertion sequences.

However, at the time the claimed invention was made inclusion of a Kozak sequence in an expression vector for optimal translation initiation of a gene in vertebrate cells was within the routine skill level of the ordinary artisan. It was also well known at the time the invention was made that an expression cassette may comprise more than one gene of interest in operable linkage with more than one promoter. For example, Meiss et al taught a vector for providing expression of a gene of interest in either prokaryotic or vertebrate cells. The vector comprised a CMV promoter in operable linkage with a Kozak sequence operably linked to a reporter gene and a sequence encoding a histidine tag. The vector also comprised a T7 promoter in operable linkage with bacterial ribosome binding site and Kozak sequence operably linked to a reporter gene and a sequence encoding a histidine tag. The Kozak sequence is interpreted to be part of the promoter since it is located upstream of the translation initiation site, in the 5' untranslated region. This interpretation has been made since the specification has not provided a definition of a promoter sequence. Also, since the reporter gene and histidine tag coding sequences are different they are interpreted to read on two separate genes of interest, which are operably linked to two different promoters as taught in the vector of Meiss et al. See Figure 1, in panel B on page 476 and also throughout pages 478 and 480. Meiss further discusses use of a CMV promoter/enhancer system.

Accordingly, in view of the teachings of Meiss et al., it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the vector of Cooper by inserting a Kozak sequence in the 5' untranslated region of a promoter such that is in operable linkage with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as it was an art-recognized goal to express a gene of interest in vertebrate cells as taught by Cooper et al, and particularly since Meiss et al specifically taught that a Kozak sequence comprising ACCATG is the optimal sequence for initiating translation in vertebrate cells and more particularly because Meiss et al created an expression vector that comprises a Kozak sequence in operable linkage with a promoter for expressing a gene of interest in a vertebrate cell (See Figure 1, in panel B on page 476 and also throughout pages 478 and 480).

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed. Claims 7, 11, 13, 14 and 18-21 appear to be free of the art of record but are subject to other rejections.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Paras, Jr. whose telephone number is 571-272-4517. The examiner can normally be reached on M-Th, 7-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (571) 272-0532.

Peter Paras, Jr.

**PETER PARAS, JR.
PRIMARY EXAMINER**



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